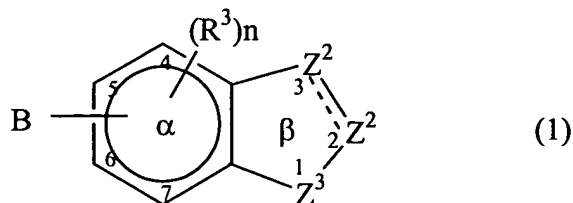


CLAIM AMENDMENTS

1. (currently amended): A compound of the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

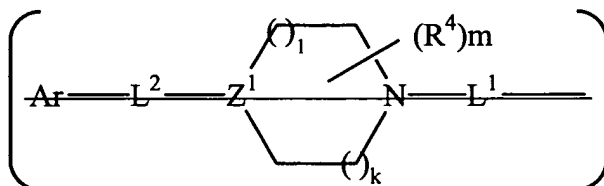
--- represents a single or double bond;

B is $-W_i-CO-X_jY$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1;

each R^3 is independently a noninterfering substituent, where n is 0-3;

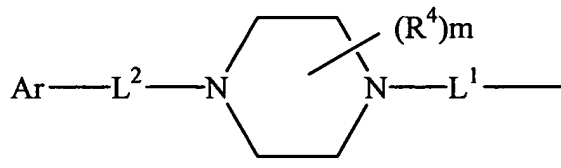
Z^3 is NR^7 or O; wherein R^7 is H or a noninterfering substituent;

one Z^2 is CA or CR^8A and the other is CR^1 , CR^1_2 , NR^6 or N wherein each R^1 , R^6 and R^8 is independently hydrogen or noninterfering substituent; wherein A is:



~~such that Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;~~

~~each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;~~



Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring;

each R^4 is independently a noninterfering substituent where m is 0-4;

each of L^1 and L^2 is a linker; and
the distance between the atom of Ar linked to L^2 and the center of the β ring is [[4.5-]] no more than 24Å.

Q' 2. (original): The compound of claim 1 wherein B is $-\text{COX}_j\text{COR}^2$, and wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2 , OCOR, NRCOR, NRCONR_2 , NRSO_2R , NRSO_2NR_2 , OCONR_2 , CN, COOR, CONR_2 , COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^2 is OR, NR_2 , SR, NRCONR_2 , OCONR_2 , or NRSO_2NR_2 , wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2 , OCOR, NRCOR, NRCONR_2 , NRSO_2R , NRSO_2NR_2 , OCONR_2 , or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is alkylene.

3. (original): The compound of claim 1 wherein Y is an isostere of COR^2 .

4. (original): The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

5. (original): The compound of claim 1 wherein each of i and j is 0.

6. (original): The compound of claim 2 wherein j is 0.

7. (original): The compound of claim 1 wherein Z^3 is NR^7 .

a 8. (original): The compound of claim 7 wherein R⁷ is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO₂R, RCO, COOR, alkyl-COR, SO₃R, CONR₂, SO₂NR₂, CN, CF₃, NR₂, OR, alkyl-SR, alkyl-SOR, alkyl-SO₂R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-CONR₂, or R₃Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

9. (original): The compound of claim 8 wherein R⁷ is H, or is optionally substituted alkyl, or acyl.

10. (canceled)

11. (original): The compound of claim 1 wherein L¹ is CO, CHOH or CH₂.

12. (original): The compound of claim 11 wherein L¹ is CO.

13-14. (canceled)

15. (original): The compound of claim 1 wherein L² is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR₂, SR, SOR, SO₂R, OCOR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, RCO, COOR, alkyl-OOR, SO₃R, CONR₂, SO₂NR₂, NRSO₂NR₂, CN, CF₃, R₃Si, and NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L² can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

16. (original): The compound of claim 15 wherein L² is unsubstituted alkylene.

17. (original): The compound of claim 15 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or $-CH=$.

Q' 18. (original): The compound of claim 1 wherein Ar is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2 , SR, SOR, SO_2R , OCOR, NRCOR, $NRCONR_2$, $NRCOOR$, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R , $CONR_2$, SO_2NR_2 , $NRSO_2NR_2$, CN, CF_3 , R_3Si , and NO_2 , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

19. (original): The compound of claim 18 wherein Ar is optionally substituted phenyl.

20. (original): The compound of claim 19 wherein said optional substitution is by halo, OR, or alkyl.

21. (original): The compound of claim 20 wherein said phenyl is unsubstituted or has a single substituent.


22. (original): The compound of claim 1 wherein R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2 , SR, SOR, SO_2R , OCOR, NRCOR, $NRCONR_2$, $NRCOOR$, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R , $CONR_2$, SO_2NR_2 , $NRSO_2NR_2$, CN, CF_3 , R_3Si , and NO_2 , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is $=O$ or an oxime, oximeether, oximeester or ketal thereof.

23. (original): The compound of claim 22 wherein each R^4 is halo, OR, or alkyl.

24. (original): The compound of claim 23 wherein m is 0, 1, or 2.
25. (original): The compound of claim 24 wherein m is 2 and both R⁴ are alkyl.
- a' 26. (original): The compound of claim 1 wherein each R³ is halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR₂, wherein R is H, alkyl, aryl, or heteroforms thereof.
27. (original): The compound of claim 26 wherein R³ is halo or alkoxy.
28. (original): The compound of claim 27 wherein n is 0, 1 or 2.
29. (original): The compound of claim 1 wherein L¹ is coupled to the β ring at the 5-position.
30. (original): The compound of claim 1 wherein Z² at position 3 is CA or CH¹A.
31. (original): The compound of claim 30 wherein the Z² at position 2 is CR¹ or CR¹₂.
32. (original): The compound of claim 31 wherein R¹ is hydrogen, or is alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR₂, SR, SOR, SO₂R, OCOR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, RCO, COOR, alkyl-OOR, SO₃R, CONR₂, SO₂NR₂, NRSO₂NR₂, CN, CF₃, R₃Si, and NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R¹ can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.
33. (original): The compound of claim 32 wherein each R¹ is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR₂, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

34. (original): The compound of claim 30 wherein Z^2 at position 2 is N or NR^6 .

a' 35. (original): The compound of claim 34 wherein R^6 is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR , SO_2R , RCO , $COOR$, alkyl-COR, SO_3R , $CONR_2$, SO_2NR_2 , CN , CF_3 , or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

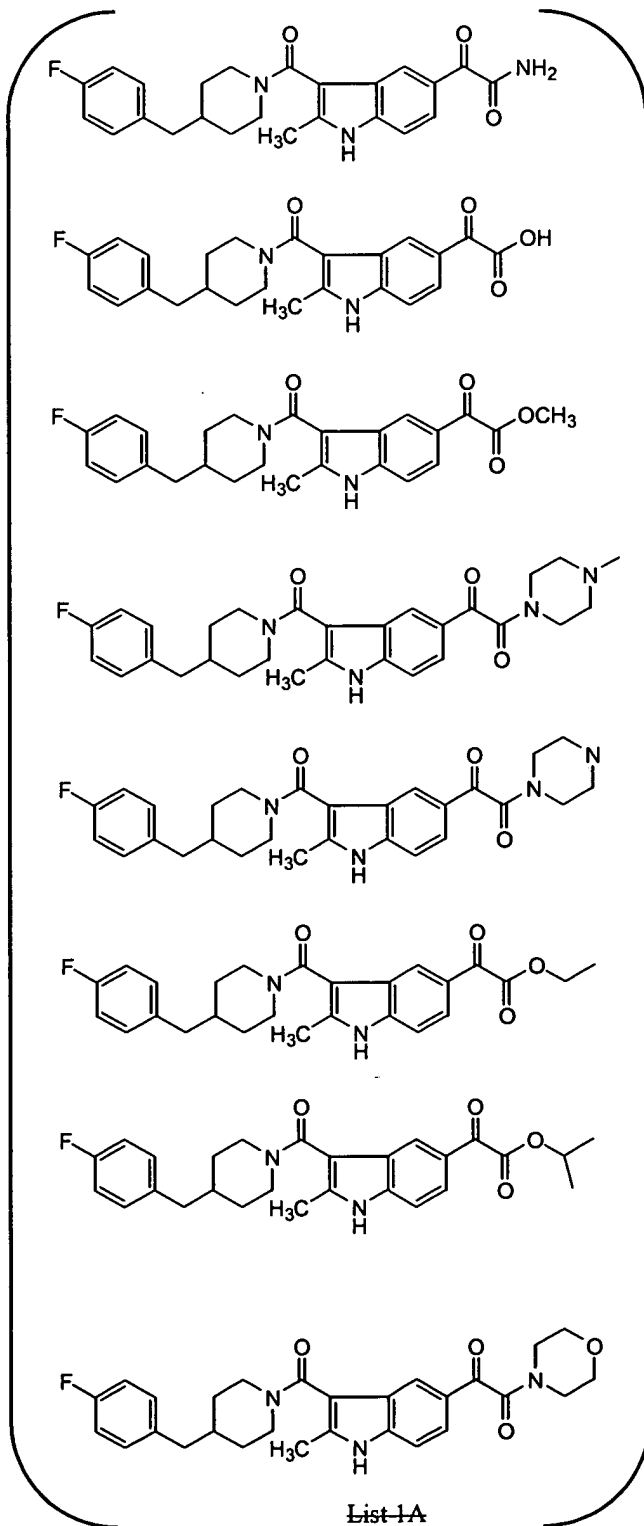
36. (original): The compound of claim 1 wherein  represents a double bond.

37. (original): The compound of claim 1 wherein the distance between the atom on Ar linked to L^2 and the center of the β ring is 7.5-11 Å.

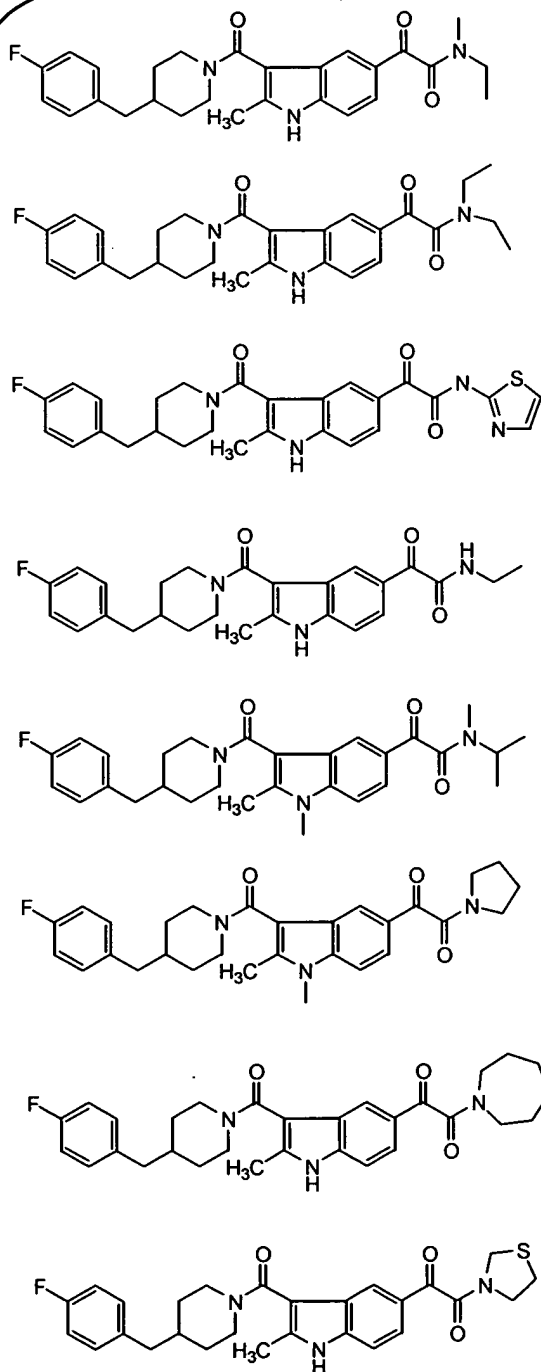
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38. (original): The compound of claim 1 wherein the compound of formula (1) is selected from the group consisting of:

Q'

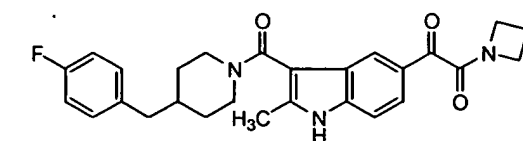
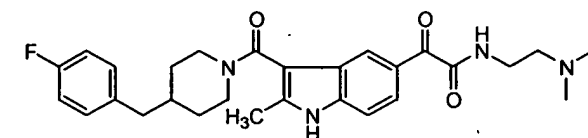
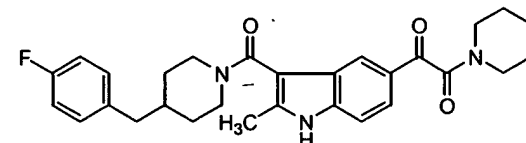
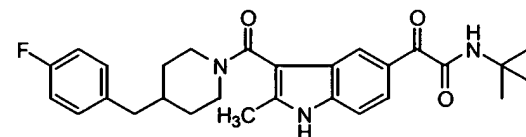
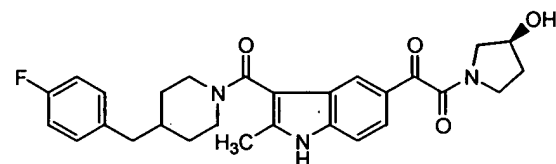
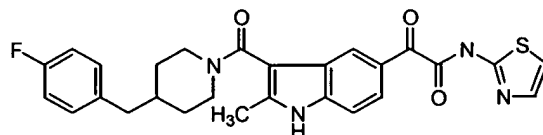
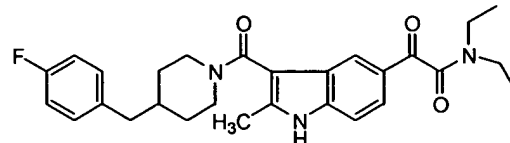
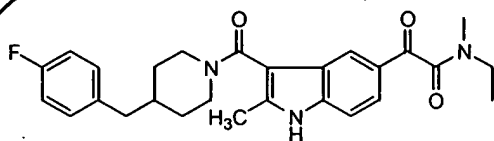


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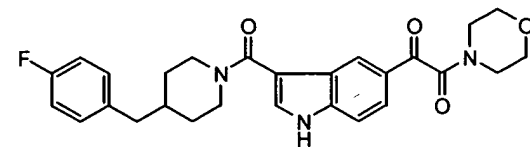
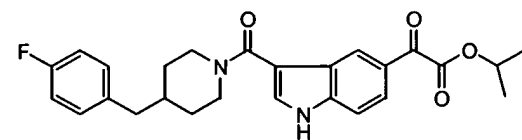
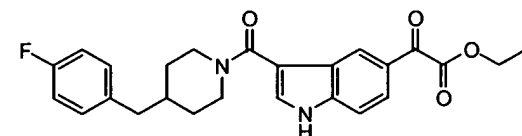
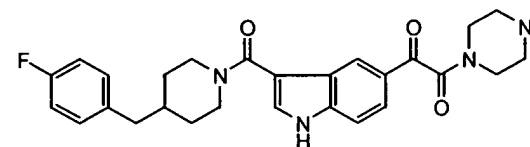
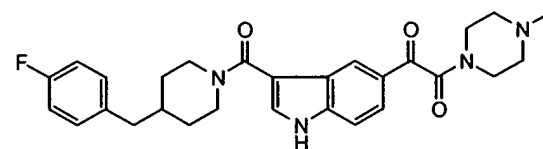
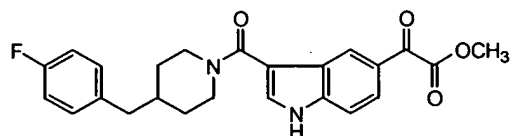
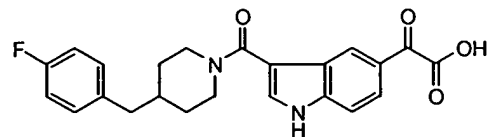
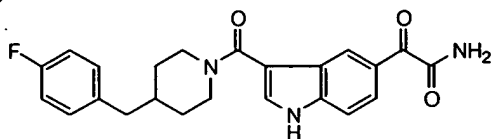
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a'



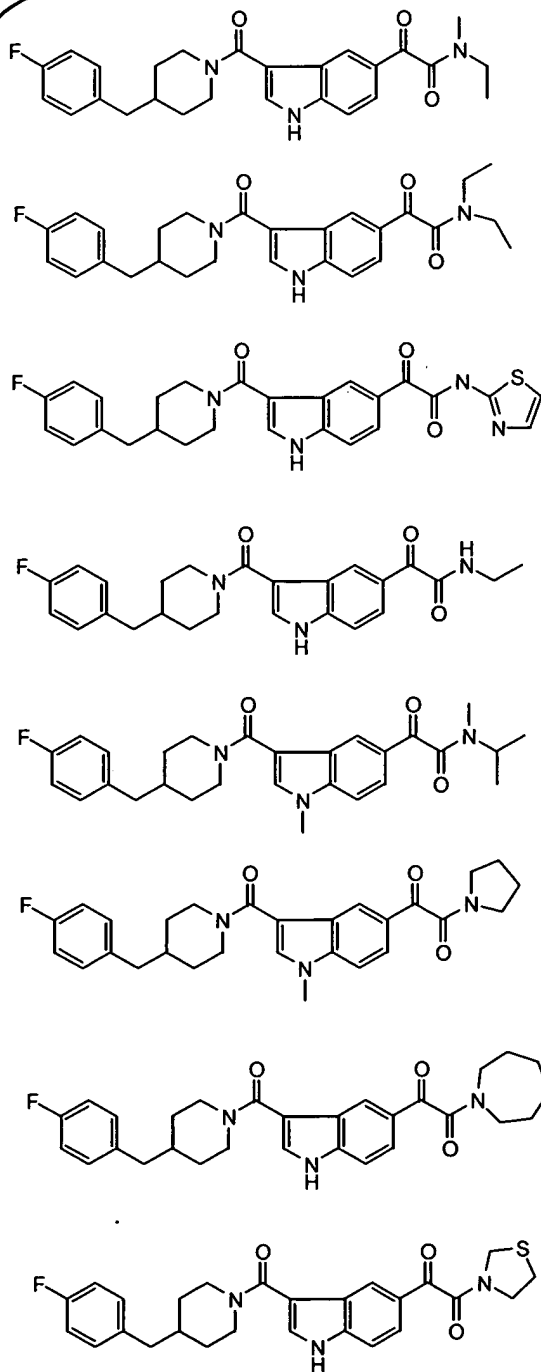
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a'



List-1D

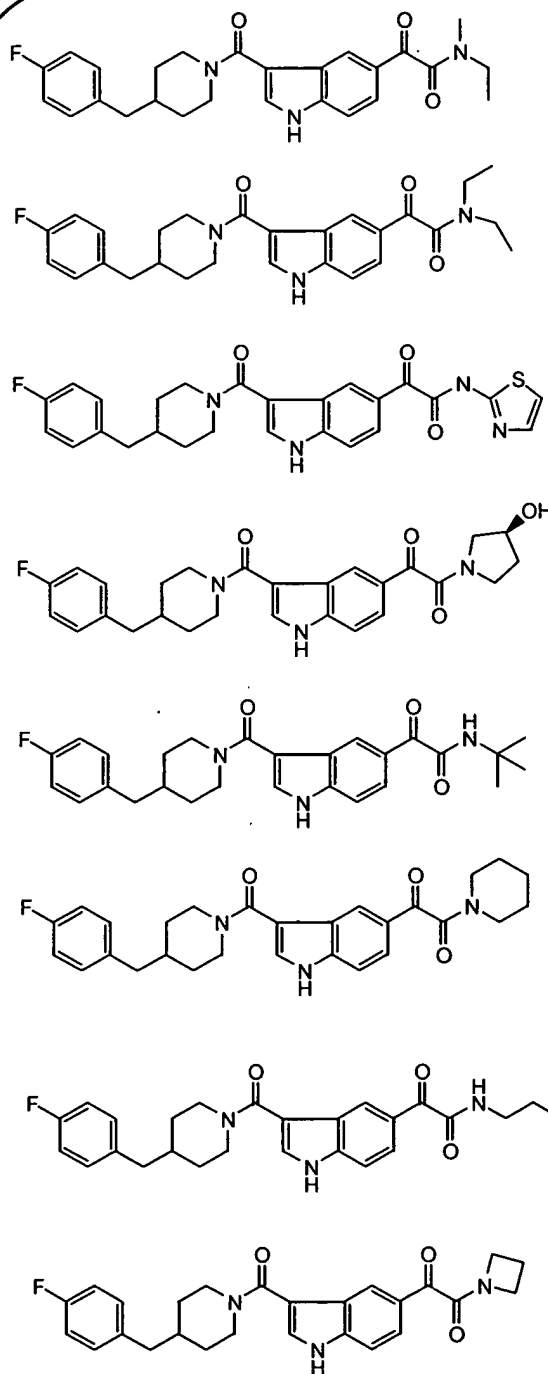
Q1



List -IE

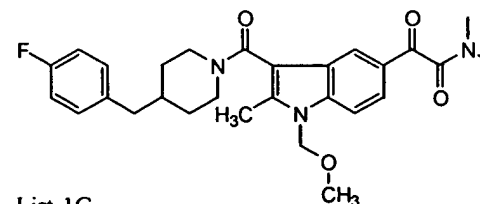
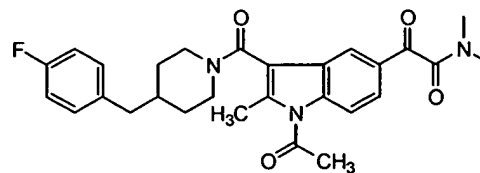
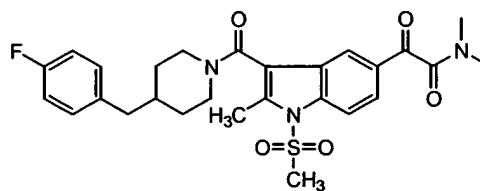
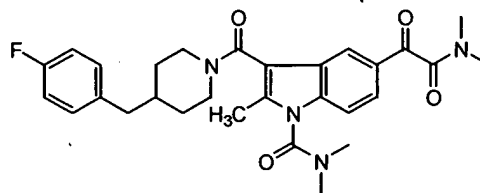
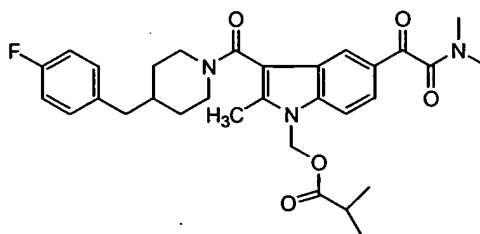
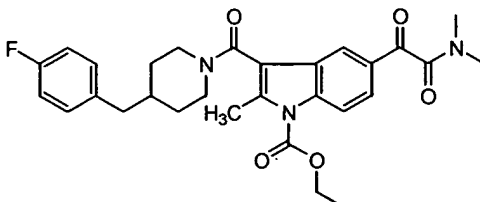
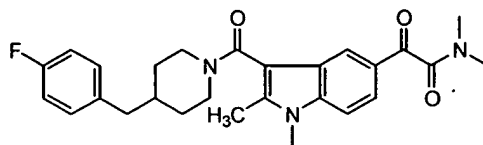
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a1



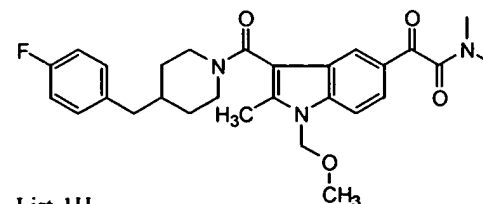
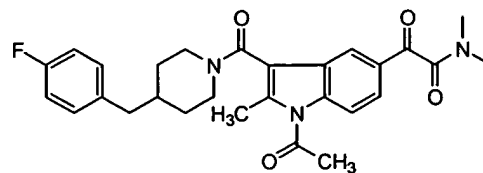
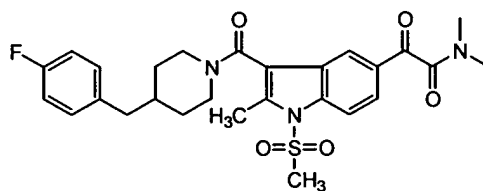
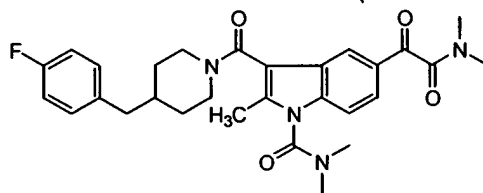
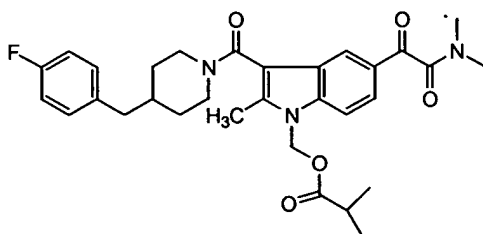
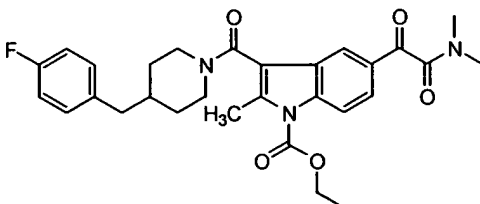
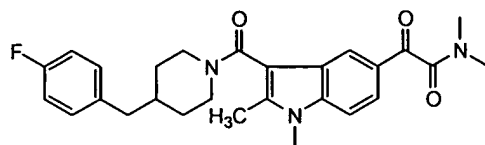
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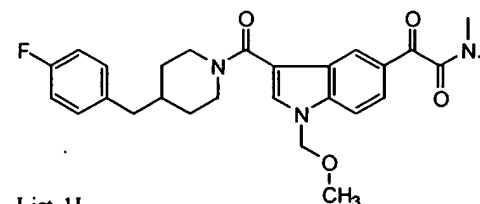
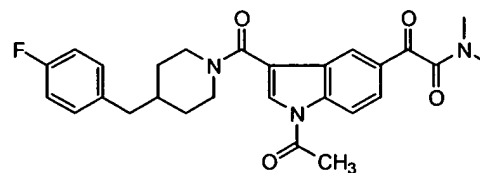
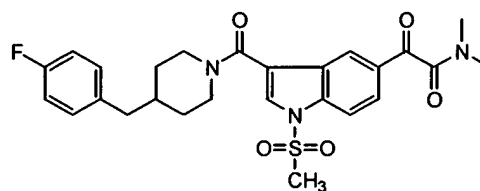
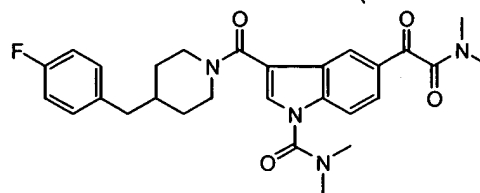
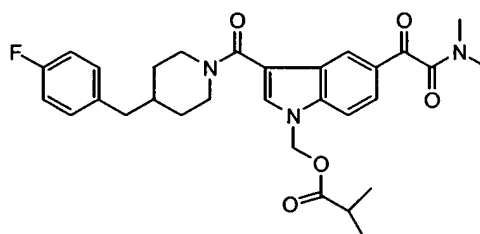
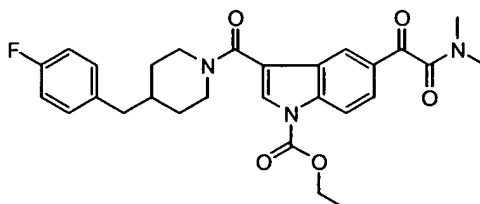
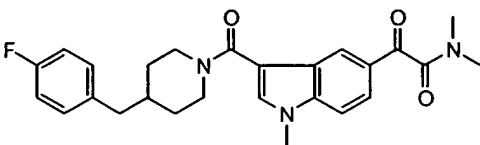
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List-1H

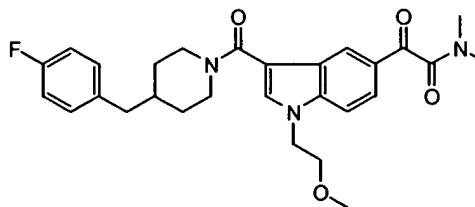
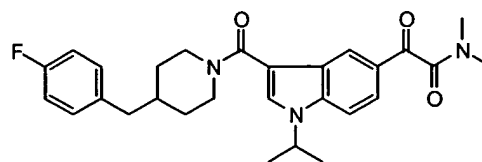
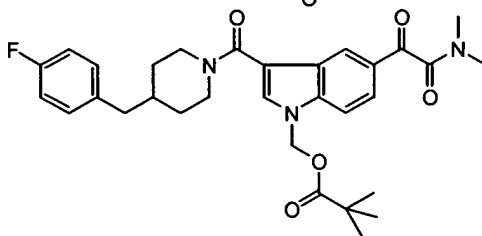
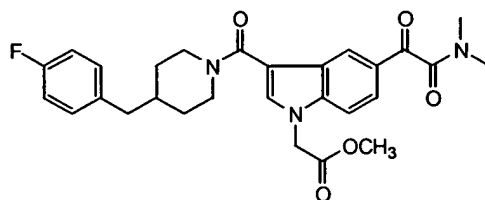
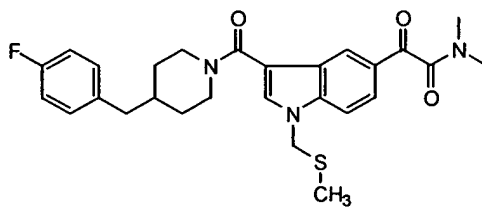
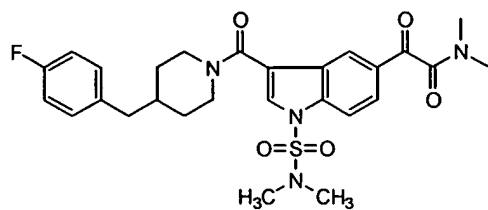
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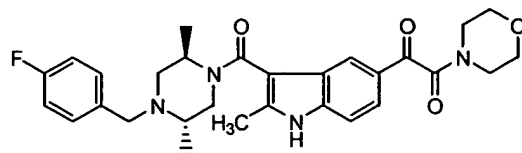
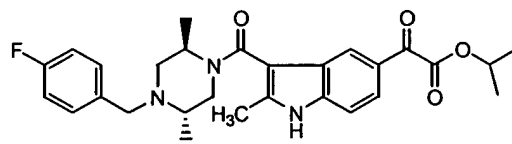
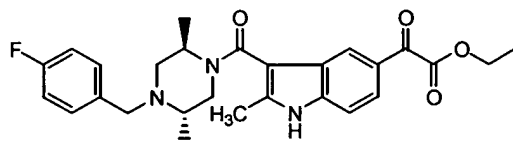
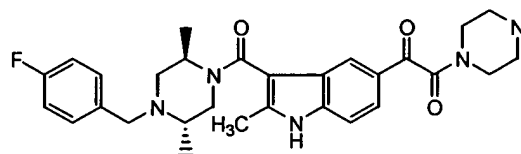
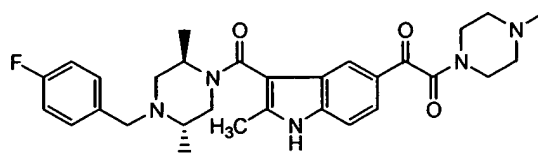
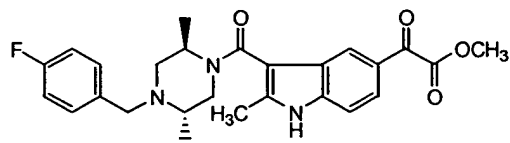
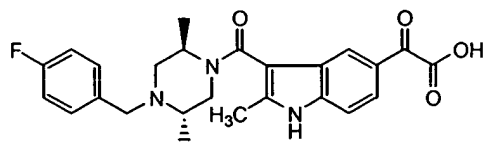
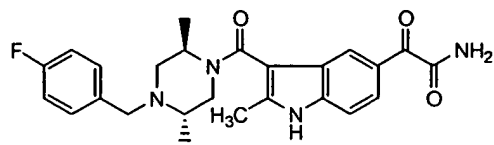
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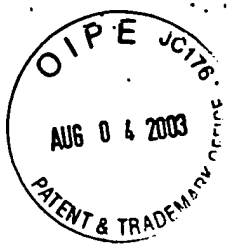
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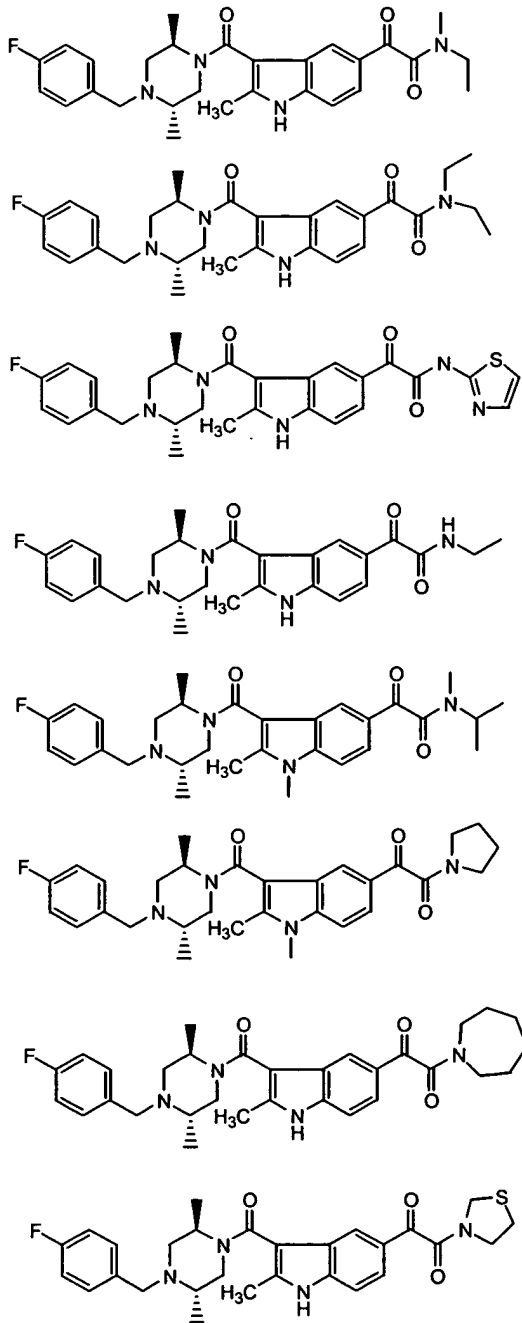
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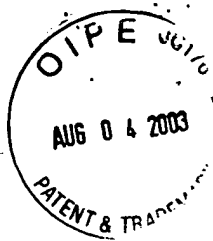
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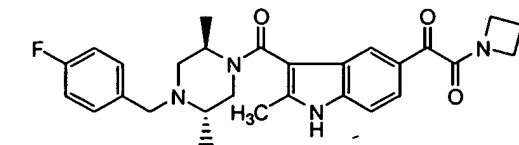
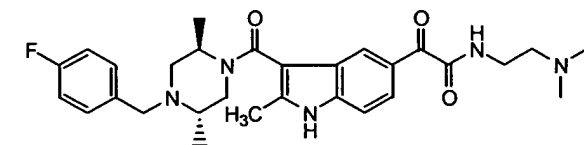
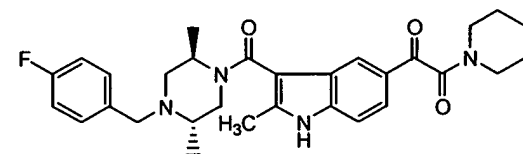
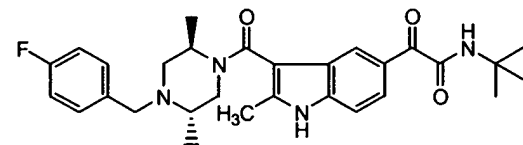
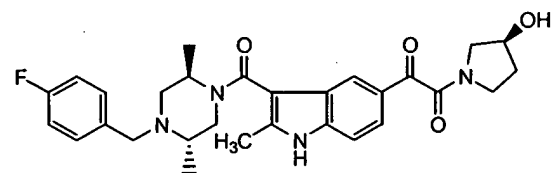
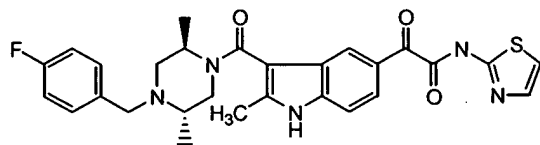
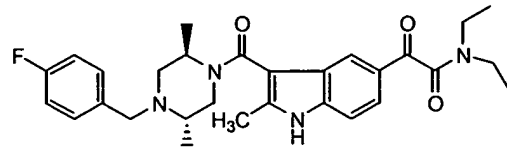
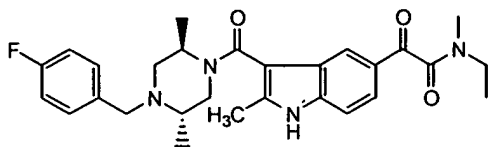
a'



List -2B



a'

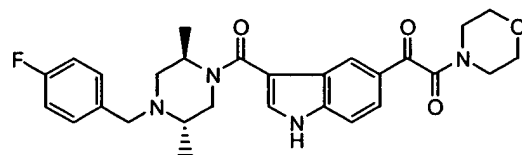
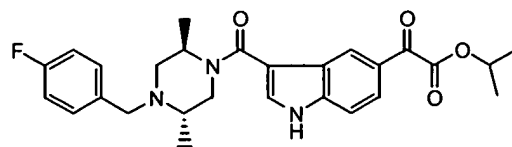
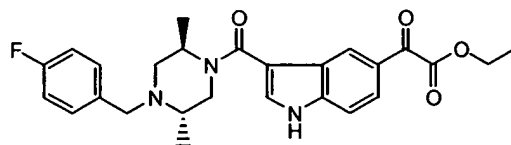
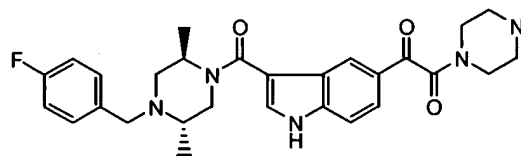
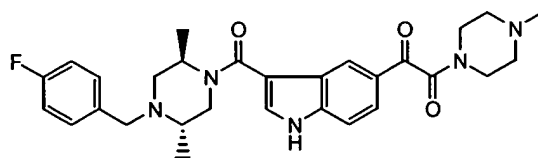
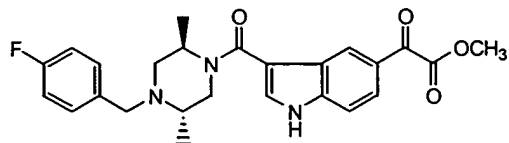
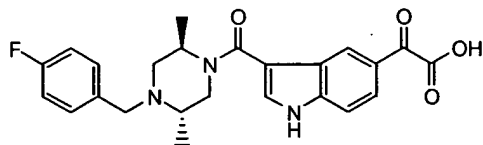
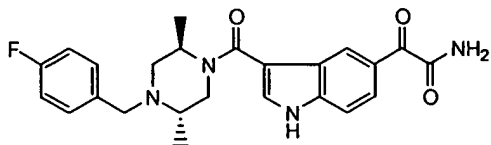


List -2C

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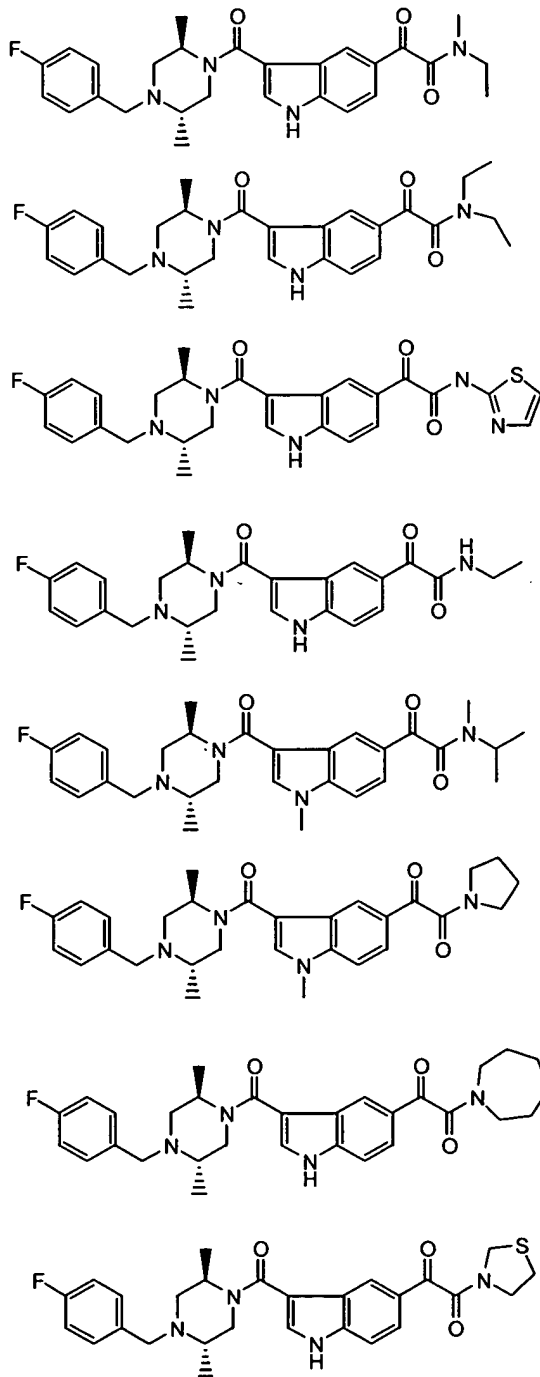


a'



List-2D

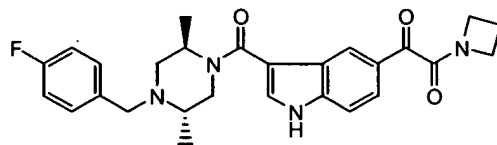
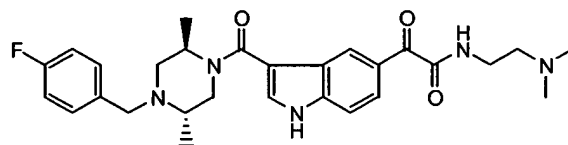
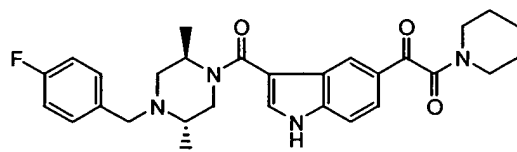
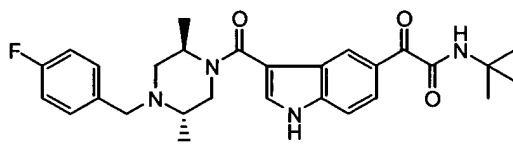
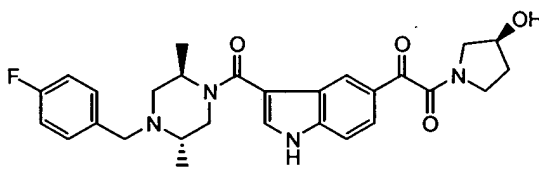
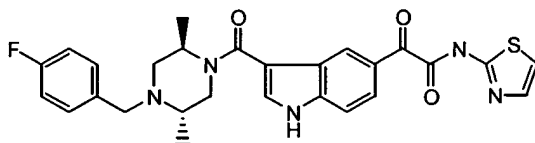
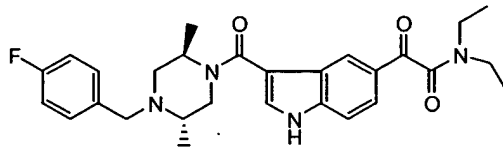
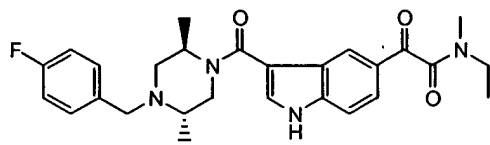
a'



List -2E

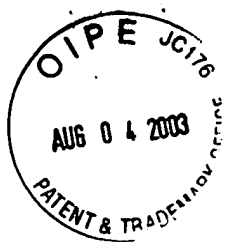


a'

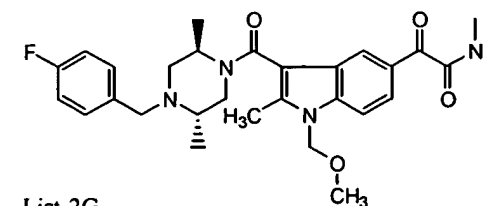
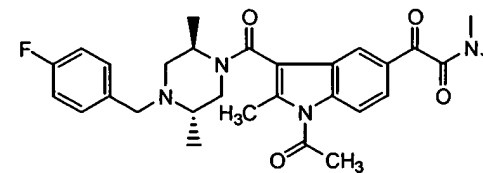
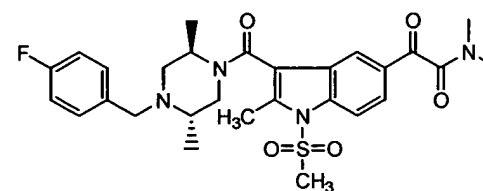
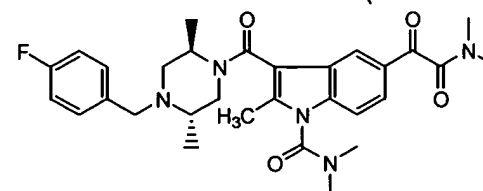
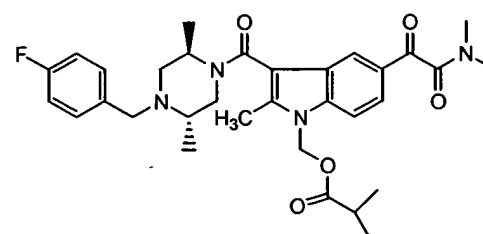
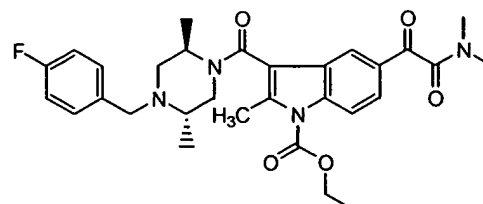
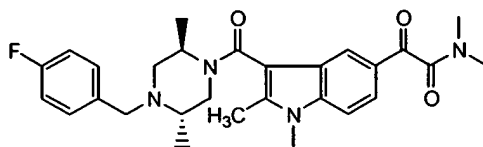


List -2F

219002029300
219002029300



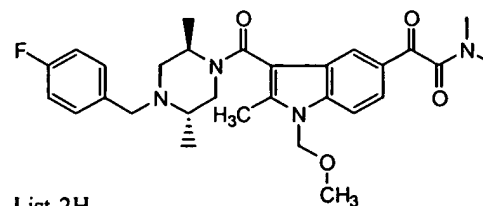
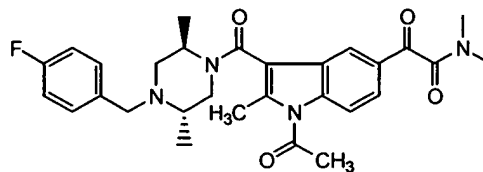
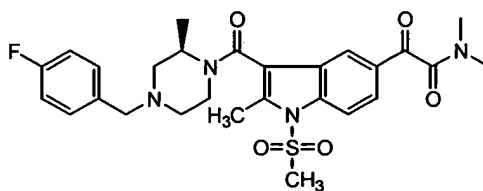
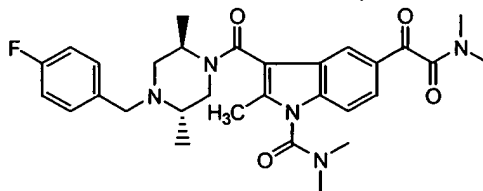
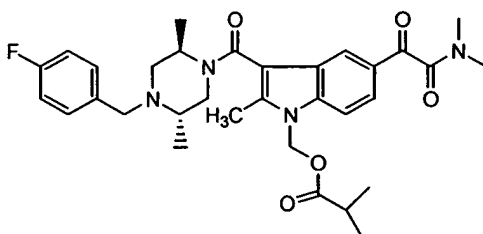
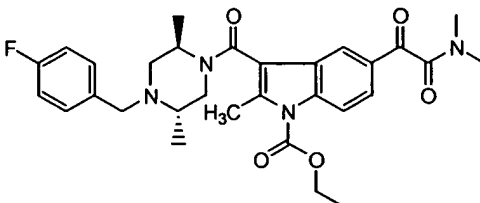
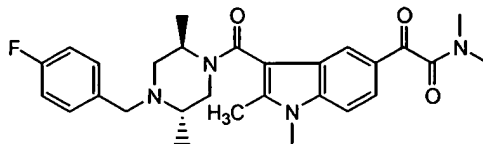
a¹



List-2G

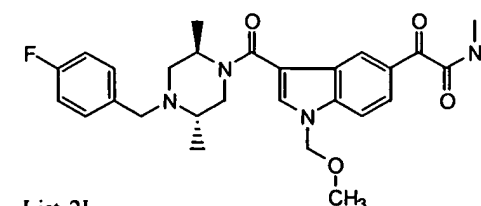
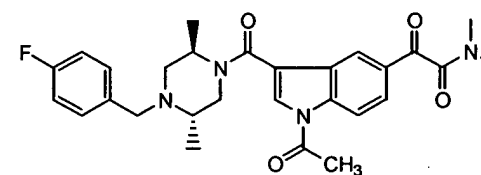
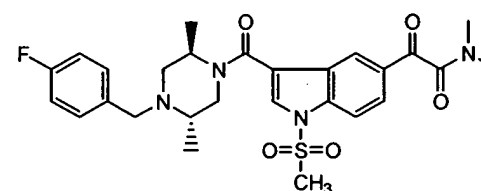
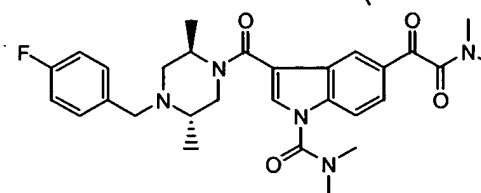
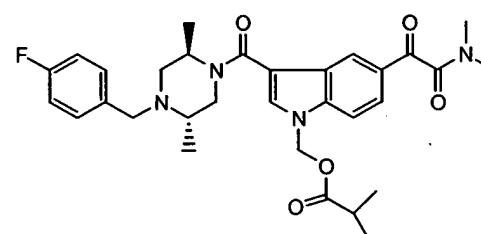
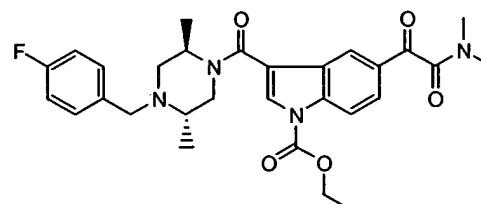
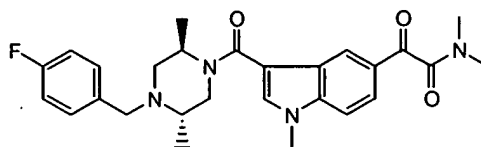
219002029300

a1



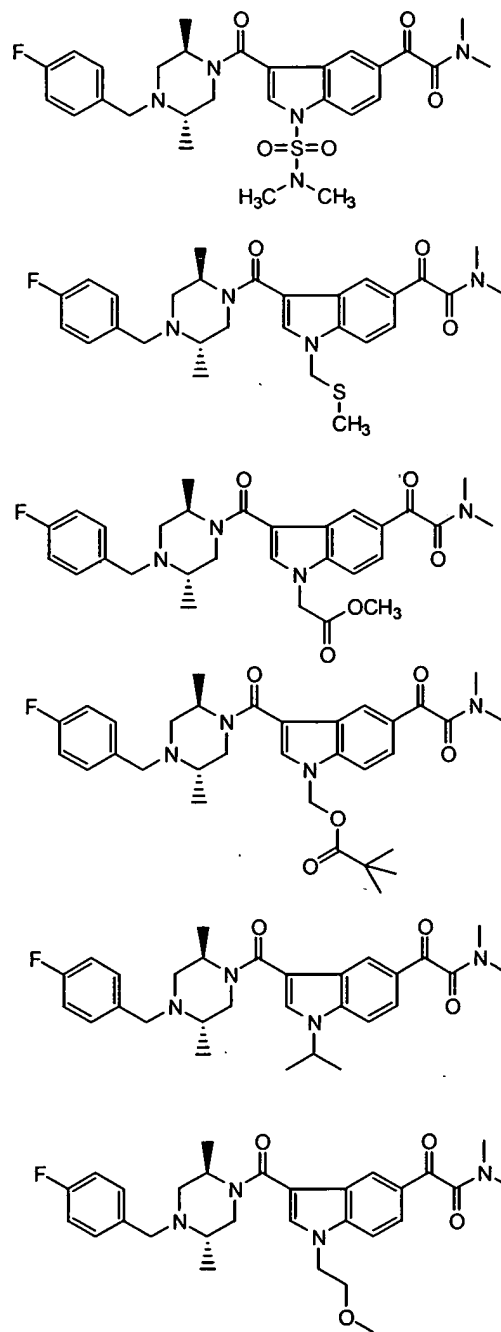
List-2H

a1



List-2I

a'

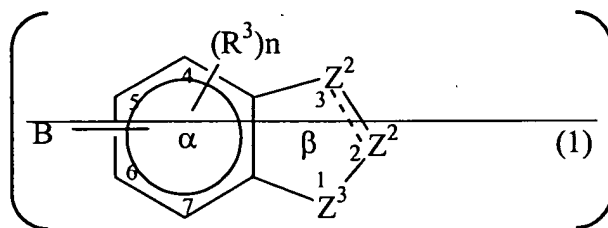


List-2J

:

39. (currently amended): A pharmaceutical composition ~~for treating conditions~~
 characterized by enhanced p38- α activity which composition comprises
 a therapeutically effective amount of ~~[[a]]~~ the compound of the formula claim 1 or a

Q1



and the pharmaceutically acceptable ~~[[salts]]~~ salt thereof in admixture with at least one
pharmaceutically acceptable carrier, ~~or a pharmaceutical composition thereof, wherein~~

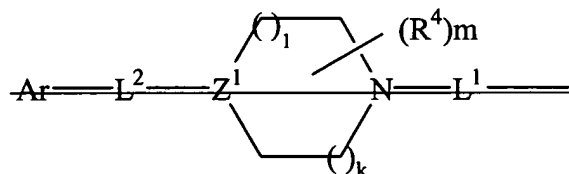
~~—~~ represents a single or double bond;

~~B is W_i-CO-X_j-Y wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a~~
~~noninterfering substituent, each of W and X is a spacer of 2-6 \AA , and each of i and j is~~
~~independently 0 or 1;~~

~~each R^3 is independently a noninterfering substituent, where n is 0-3;~~

~~Z^3 is NR^7 or O; wherein R^7 is H or a noninterfering substituent;~~

~~one Z^2 is CA or CR^8A and the other is CR^1 , CR^2 , NR^6 or N wherein each R^1 , R^6 and R^8 is~~
~~independently hydrogen or noninterfering substituent; wherein A is:~~



~~such that Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;~~

~~each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;~~

~~Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two~~
~~noninterfering substituents can form a fused ring;~~

~~each R^4 is independently a noninterfering substituent where m is 0-4;~~

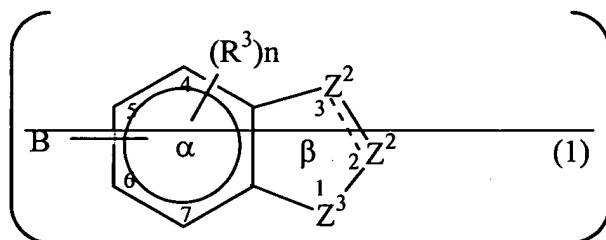
~~each of L^1 and L^2 is a linker; and~~

~~the distance between the atom of Ar linked to L^2 and the center of the β ring is 4.5-24 \AA .~~

40. (original): The composition of claim 39 which further contains an additional
 therapeutic agent.

41. (original): The composition of claim 40 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

a' 42. (currently amended): A method to treat a condition mediated by p38- α kinase comprising administering to a subject in need of such treatment a compound of the formula claim 1 or:



and the a pharmaceutically acceptable [[salts]] salt thereof, or a pharmaceutical composition thereof, wherein

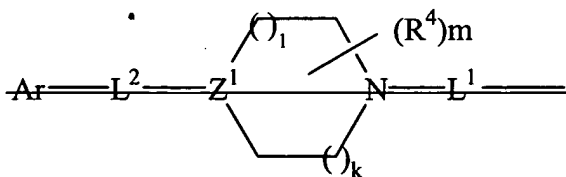
~~—~~ represents a single or double bond;

B is W_iCOX_jY wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1;

each R^3 is independently a noninterfering substituent, where n is 0-3;

Z^3 is NR^7 or O; wherein R^7 is H or a noninterfering substituent;

one Z^2 is CA or CR^8A and the other is CR^1 , CR^2 , NR^6 or N wherein each R^1 , R^6 and R^8 is independently hydrogen or noninterfering substituent; wherein A is:



such that Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;

each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring;

each R^4 is independently a noninterfering substituent where m is 0-4;

each of L^1 and L^2 is a linker; and

the distance between the atom of Ar linked to L^2 and the center of the β ring is 4.5-24Å.

43. (original): The method of claim 42 wherein said condition is a proinflammation response.

a¹ 44. (currently amended): The method of claim 43 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, ~~septic shock~~, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, ~~stroke~~, reperfusion injury, ~~CNS injury~~, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's or pyresis.
